REMARKS

In view of the following remarks, the Examiner is requested to withdraw the rejections and allow Claims 1-16 and newly presented Claims 26-34, the only claims pending and currently under examination in this application.

Formal Matters

Claims 1-16 were examined and rejected.

Claims 1 and 2 have been amended in order to provide explicit antecedent basis for the limitations recited in the Office Action.

Claim 1 has been further amended to specify that each of the at least 20 distinct control target nucleic acids **is known to be complementary to a probe nucleic acid present on the array**. Support for this amendment can be found throughout the specification, for example at p. 6, lines 1-15.

Claims 26-34 have been newly added and find support throughout the specification and original claims, for example, at p. 5, lines 25-30, and original claims 1-7 and 10-11.

Claims 17-25 have been canceled.

As the above amendments enter no new matter to the application, their entry is respectfully requested.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1-16 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regards as the invention.

Claims 1-16

According to the Office Action, the recitation of "said control pool of target nucleic acids" in Claim 1 lacks proper antecedent basis. In addition, the recitation of "at least 20 distinct target nucleic acids" is unclear as to whether the claim is referring to the test set of target nucleic acids or the control set of target nucleic

acids. In view of the above amendments to Claim 1, these rejections may be withdrawn.

Claims 2-3 and 7

The Examiner alleges that Claims 2-3 and 7 are indefinite over the recitation "at least a subset of the probe nucleic acids present on said array" because the phrase "the probe nucleic acids" in Claim 2, lacks antecedent basis. In view of the above amendment to Claim 2, this rejection may be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1-6, 8-10, 13-14 and 16 have been rejected under 35 U.S.C. § 102(a) and102 (e) as being anticipated by Brown et al. (U.S. Patent No. 5,807,522).

According to MPEP § 2131:

In order to anticipate a claim, the cited reference must teach all of the limitations of the claimed invention.

Claim 1 of the present invention specifies that a control set of target nucleic acids comprises at least 20 distinct control target nucleic acids wherein each of the at least 20 distinct control target nucleic acids is of **known sequence and present in known amount and known to be complementary to a probe nucleic acid present on the array.**

As such, an element of the present invention is that the control set of target nucleic acids includes nucleic acids that are of **known sequence** and **present in known amount** and **known to be complementary** to probe nucleic acids on the array.

In contrast, Brown et al. discloses methods of detecting differential expression of each of a plurality of genes in a first cell type (e.g. transgenic sample), with respect to expression of the same genes in a second cell type (e.g. wild type

sample). Differences between the resultant hybridization patterns are then detected and related to differences in gene expression between the two samples.

In making the rejection, the Examiner asserts the following:

> In the event that the **transgenic plant sample** was considered to be **the control sample**, all of the **spots (probe nucleic acids present on the array) would have appeared in the control sample** (Office Action, p. 5) (emphasis added).

According to the Office Action, it appears that the Examiner is equating the targets from one sample (e.g. transgenic) to be the equivalent of the Applicants' control set of target nucleic acids having at least 20 distinct control target nucleic acids of **known sequence** and **present in known amount** and **known to be complementary to probe nucleic acids on the array**.

However, Brown et al. is describing a method of differential gene expression. As such, prior to the detection step, one does not know the sequence or amount of the targets from either of the cell types, let alone whether any of the targets are complementary to a probe nucleic acid on the array. Therefore, neither sample is equivalent to the presently claimed control set of target nucleic acids regardless of which sample is designated the "control sample."

As such, the Applicants submit that Brown et al. fails to teach the element of a control set of target nucleic acids having at least 20 distinct control target nucleic acids of **known sequence** and **present in known amount** and **known to be complementary to probe nucleic acids on the array**. Accordingly, this rejection may be withdrawn.

Claims 1, 4-10, 13, 16, and 26-34 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Bao et al. (U.S. Patent No. 6,251,601).

The Applicants note that prior to this response, Claims 1-25 were the only

claims pending in the present application. Therefore, the Applicants respond to this rejection with respect to Claims 1, 4-10, and 12-16.

As discussed above, an element of the present invention is that the control set of target nucleic acids include nucleic acids that are of known sequence and in known amount and **known to be complementary to a probe nucleic acid.**

The present application describes a probe nucleic acid as follows:

> **The term "probe nucleic acid" refers to nucleic acids stably associated with the surface of a solid support which correspond to a target gene of interest in a sample. Probe nucleic acids are not random nucleic acids or nucleic acids that correspond to genes that are not of interest in a sample, e.g., housekeeping genes, genes that are widely expressed among tissues, etc.** (Office Action, p. 5) (emphasis added).

As such, the control set of target nucleic acids include nucleic acids that are complementary to **probe nucleic acids where probe nucleic acids are defined as nucleic acids which correspond to a target gene of interest in the sample.**

In contrast, Bao et al. teaches a method of differential gene expression in which targets from three sources are simultaneously added to an array. The first two sources are "test" samples and the third source is a "reference" sample. Bao et al. further teaches that the "spiked" known amount of a particular genomic or cDNA sequence is added to the reference sample for control analysis.

Turning now to the rejection, the Examiner asserts the following in the Office Action:

> Bao teaches that the reference nucleic acids can be **"spiked; to include a known amount of a particular genomic or cDNA sequence**, i.e., known amount and known sequence for each of the controls (Office Action, p. 7) (emphasis added).

In making the rejection, it appears that the Examiner is equating the "spiked" reference nucleic acids of Bao et al. with the control set of target nucleic acids of the present invention.

However, as set forth above, the control set of target nucleic acids of the present invention include nucleic acids of known sequence and in known amount and known to be complementary to probe nucleic acids on the array where a probe nucleic acid is defined as a nucleic acid which **corresponds to a target gene of interest in a sample.**

The Examiner has not shown where Bao et al. teaches that his "spiked" reference nucleic acids are complementary to **probe nucleic acids that correspond to a target gene of interest in the sample as in the present invention.**

As such, contrary to the Examiner's assertion, the "spiked" reference nucleic acids of Bao et al. are not the equivalent of the **control set of target nucleic acids as presently claimed.**

Therefore, Bao et al. fails to teach each and every element of the present invention. Accordingly, the rejection of Claims 1, 4-10, 13, and 16 under 35 U.S.C. § 102(e) over Bao et al. may be withdrawn.

Rejection under 35 U.S.C. §103

In the Office Action, Claims 7 and 15 have been rejected under 35 U.S.C. §103 (a) as being obvious over Brown et al. (U.S. Patent No. 5,807,522).

With respect to rejections made under 35 U.S.C. § 103, MPEP § 2142 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

> Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.1991) [emphasis added].

As discussed above, Brown et al. fails to teach the element of a control set of target nucleic acids having nucleic acids of **known sequence** and **present in known amount** and **known to be complementary to probe nucleic acids on the array.** As such, Brown et al. does not teach or suggest each and every element of Claim 1.

Because Claims 7 and 15 depend from Claim 1, these claims include the element of a control set of target nucleic acids having at least 20 distinct control target nucleic acids of **known sequence** and **present in known amount** and **known to be complementary** to probe nucleic acids present on the array.

Therefore, for at least the reasons discussed above, Brown et al. does not teach or suggest each and every element of Claims 7 and 15. Accordingly, this rejection may be withdrawn.

Claims 1-16 have been rejected under 35 U.S.C. §103 (a) as being obvious over Lockhart et al. (U.S. Patent No. 6,040,138) in view of Brown et al. (U.S. Patent No. 5,807,522).

In making the rejection, the Examiner asserts the following:

> Normalization probes can be localized at any position in the array or at multiple positions throughout the array to control for spatial variation in hybridization efficiently, especially at the corners or edges of the array. **Lockhart teaches adding the normalization control probes complementary to control sequences in a known concentration to the sample** (Office Action, p. 12)

(emphasis added).

It seems that the Examiner is equating Lockhart's **target control sequences** which are **complementary to the normalization probes** with the Applicants' control set of target nucleic acids.

However, as discussed above, the presently claimed control set of target nucleic acids include nucleic acids that are of known sequence and in known amount and known to be complementary to probe nucleic acids on the array. According to the present application, a probe nucleic acid is defined as a nucleic acid stably associated with the surface of a solid support which **corresponds to a target gene of interest in a sample.** The instant specification goes on to specify that probe nucleic acids are **not random nucleic acids** or nucleic acids that correspond to genes **that are not of interest in a sample**, e.g., housekeeping genes, genes that are widely expressed among tissues, etc.

In contrast to the present invention, Lockhart describes his normalization controls as follows:

> Normalization controls are oligonucleotide probes that are **perfectly complementary to labeled reference oligonucleotides that are added to the nucleic acid sample** (col. 16, lines 1-14) (emphasis added).

As such, Lockhart's normalization control probes are complementary to the reference oligonucleotides in the target sample. Unlike the present invention, the normalization control probes do not correspond to a target gene of interest in the sample.

Therefore, Lockhart et al. fails to teach or suggest each and every element of the present application.

Additionally, as noted above, Brown et al. fails to teach or suggest the element of a control set of target nucleic acids having at least 20 distinct control

target nucleic acids of **known sequence** and **present in known amount** and **known to be complementary to probe nucleic acids** present on the array.

Because the cited combination of references fails to teach each and every element of the claimed invention, it is respectfully submitted that Claims 1-16 are not obvious under 35 U.S.C. § 103(a) over Lockhart et al. in view of Brown et al. Accordingly, this rejection may therefore be withdrawn.

Claims 1, 4-10, 12-16, and 26-34 have been rejected under 35 U.S.C. §103 (a) as being obvious over Bao et al. (U.S. Patent No. 6,251,601).

The Applicants note that prior to this response, Claims 1-25 were the only claims pending in the present application. Therefore, the Applicants respond to this rejection with respect to Claims 1, 4-10, and 12-16.

As set forth above, Bao et al. fails to teach the element of the present invention in which a control set of target nucleic acids having at least 20 distinct control target nucleic acids **known to be complementary to probe nucleic acids** present on the array, where a probe nucleic acid is defined as a nucleic acid that **corresponds to a target gene of interest in a sample.**

As such, Bao et al. fails to teach or suggest each and every element of the present invention.

Therefore, the Applicants submit that Claims 1, 4-10, and 12-16 are not obvious over Bao et al. Accordingly, this rejection may be withdrawn.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CLON-012CIPCON.

Respectfully submitted,

Date: 3-28-06

By: Geri N. Rochino
Geri N. Rochino
Registration No. 58,147

Date: 3.28.06

By:
Bret E. Field
Registration No. 37,620

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Circle, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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